Computational Molecular Modeling of the Binding of Environmental Molecules to Biological Receptors, Modeling a Mechanism of Toxicity, the Estrogen Receptor

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Anthropogenic chemicals may disrupt the normal activity of biological systems by (partially) mimicking endogenous functional biological molecules, like hormones and other signal transmitters, and interfering with recognition processes. In order to understand and predict the capacity of environmental chemicals to act through this type of mechanism, computational molecular models for specific molecular biorecognition processes are being developed. Initial emphasis is being placed on the binding of natural and environmental ligands to the estrogen receptor. There are a number of examples of experimentally determined three-dimensional structures for the estrogen receptor with a ligand bond. Starting from these structures, the ligand is removed computationally and a three-dimensional pattern for the receptor is obtained. For a chemical to interact with the receptor (and mimic the natural ligand) it must be complementary with the interaction pattern of the receptor. One element of this complementarity is the molecular fit in the cavity that remains after the removal of the natural ligand. Another element is its capacity for complementary physicochemical properties. These protein cavities in general and the estrogen receptor in particular have complex shapes and interaction patterns. In order to deal with this complexity, computational methods have been developed to "dock" a potential ligand into this protein cavity. In this study, potentially estrogenic metabolites of polycyclic aromatic hydrocarbons (PAH), a class of environmental chemicals, and other similar molecules have been “docked” into the estrogen receptor. Results of docking indicate that some metabolites are potential environmental estrogens. The results obtained in this manner show wide variation in potential activity for specific molecules. They depend on PAH type and the three-dimensional structure of the metabolite. For example (-)-anti-benzo[c]phenanthrene diolepoxide is a much better binder in this model than the (+) enantiomer. These results will be compared to the results for known binders. Examination of the three dimensional structures obtained and additional higher level molecular calculations allow the determination of the forces and features that are important for binding to the estrogen receptor and the complementary forces and features that enable environmental chemicals to interact with the receptor. This general method is applicable to other biorecognition processes and the interaction of chemicals with DNA. These methods have potential application to other environmental problems.

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